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14. ABSTRACT The overall goal of the study is to examine whether altered vitamin D status (as measured by serum metabolites and by functional polymorphisms within genes related to vitamin D transport, metabolism and activity) is associated with increased risk of aggressive prostate cancer, and may explain some of the racial disparity seen in aggressive prostate cancer. The majority of project activities as outlined in the Statement of Work Tasks and Milestones are complete. The study team has been organized and participates in monthly conference calls (or more frequent as needed) to discuss study progress and data collection and analyses. IRB approval was obtained from all local institutions and the DoD HSRRB. All assays have been performed and data have been merged and cleaned. Statistical analyses are underway. With the large representation of African Americans in this investigation, the proposed research has tremendous potential to provide insights into a chronically underserved population carrying an unequal burden of disease.					
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INTRODUCTION:

Experimental and ecologic studies support a role of vitamin D in prostate cancer prevention and prognosis; however, epidemiologic study results are inconsistent. Altered vitamin D status (as measured by plasma metabolites and by functional polymorphisms within genes related to vitamin D transport, metabolism and activity) is hypothesized to be associated with increased risk of aggressive prostate cancer, and may explain some of the racial disparity seen in aggressive prostate cancer. It is also hypothesized that plasma parathyroid hormone (PTH), serum calcium and serum phosphorus levels are inversely and directly correlated with plasma 25(OH)D and 1,25(OH)₂D levels, respectively, and are positively associated with disease aggressiveness. Polymorphisms within ten genes involved in vitamin D transport, metabolism and activity will be examined to determine whether 1) allele and genotype frequencies differ by race, 2) plasma vitamin D metabolite concentrations are related to polymorphisms in these genes, 3) allele and genotype/haplotype frequencies are different in more aggressive disease as compared to less aggressive disease, and 4) vitamin D and genetic polymorphisms act synergistically to affect prostate cancer aggressiveness. We will examine these associations among vitamin D status, PTH, calcium, phosphorus, polymorphisms in vitamin D-related genes, and prostate cancer aggressiveness in the North Carolina-Louisiana Prostate Cancer Project (PCaP), a previously-conducted case-only study of prostate cancer among equal numbers of African Americans and European Americans. New laboratory data will be generated using previously-collected biospecimens from PCaP, and data will be analyzed using epidemiologic techniques for estimating odds of high aggressive prostate cancer according to vitamin D, PTH, calcium, phosphorus and genetic polymorphisms.

BODY:

The majority of project activities, as outlined in the Statement of Work (SOW) Tasks and Milestones, have been completed and ongoing work is focused on continued data analyses and manuscript development. A 12-month no-cost extension was requested and granted, so the new end date for the grant is September 29, 2015.

Activities in Task #1, the run-in phase of months 1-6, have been accomplished as described in more detail below. The majority of activities related to Task #2 (planned to occur in months 7 to 24 of the grant award period) and Task #3 (planned to occur in months 25-36) have been accomplished as outlined below, with ongoing data analyses and manuscript development continuing into the no-cost extension year. Below please find the original SOW activity listed in the numbered bullet, and the progress and status of those activities listed in the indented lettered bullet underneath each activity.

Task 1: Run-in Phase, Months 1-6:

1. Organize the investigative team and schedule regular conference calls between investigators
 - a. Conference calls have been occurring once per month or more often as needed
2. Obtain IRB approval for the study from all institutions and DoD HSRRB
 - a. IRB approval was granted by each of the institutions (USC, Roswell Park Cancer Institute, UCLA, and UNC-CH) and by DoD HSRRB
3. Complete the data acquisition form from the parent PCaP Study
 - a. Data was requested and obtained from PCaP
4. Develop a Manual of Operations (MOP), a detailed document describing data transfer, data merging, and data management systems. The MOP content is based on our successful experience with other large-scale epidemiologic studies.
 - a. A system of data transfer has been developed, and the MOP has been assembled.
5. Arrange for shipment of 1,200 serum samples to Roswell Park for vitamin D analyses, 1,200 plasma and 1,200 DNA samples to USC for PTH analyses and genotyping, and serum samples to UCLA for calcium (1,200 samples) and phosphorus (1,200 samples) analyses

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- a. It was decided that plasma samples were more appropriate for vitamin D analyses, instead of serum samples, because the plasma samples were collected and transported under light-protected conditions.
 - b. It was decided that genotyping would be conducted by Roswell Park Cancer Institute Shared Genomic Resources facility due to their having the appropriate technology and experience for the Illumina Goldengate and Sequenom genotyping methodology being used.
 - c. Plasma samples and DNA samples were shipped from UNC-CH to Roswell Park, serum samples were shipped to UCLA, and plasma samples were shipped to USC.
6. Drs. Steck and Johnson attend PCRP IMPaCT Annual Meeting or other scientific meeting.
- a. There was not an IMPaCT meeting in Year 1. Dr. Steck attended the American Society of Preventive Oncology meeting in March 2012

All milestones for Task #1 were met (IRB and HSRRB approval, samples aliquotted and shipped to labs, data systems in place for capture of all data from different sources).

Task 2: Laboratory Analyses, Interim Data Analyses, Months 7-24:

1. Conduct plasma 25(OH)D and 1,25(OH)₂D lab measurements at Roswell Park Cancer Institute
 - a. Plasma vitamin D metabolite measurements are complete.
2. Conduct genotyping at Roswell Park Cancer Institute Shared Genomics Resource facility
 - a. Genotyping was completed at Roswell Park Cancer Institute using Illumina Goldengate and Sequenom methodology.
3. Conduct plasma PTH measurements at Psychoneuroimmunology Lab at USC
 - a. Plasma PTH measurements are complete
4. Conduct serum calcium and phosphorus measurements at UCLA
 - a. Serum calcium and phosphorus measurements are complete.
5. Hire graduate assistant at USC
 - a. A senior-level doctoral student, Sam Antwi, was hired as a GA.
6. Have all raw data sent to USC and to PCaP parent study
 - a. Raw data from Roswell Park and UCLA have been distributed to USC. Data generated from the study will be sent to PCaP at the end of the study.
7. Manage data, begin cleaning data as it becomes available
 - a. Data from PCaP, Roswell Park, UCLA, and USC have been merged and cleaned.
8. Drs. Steck and Johnson attend PCRP IMPaCT Annual Meeting or other scientific meeting.
 - a. There was no IMPaCT meeting in Year 2. Dr. Steck attended the American Association for Cancer Research Frontiers in Cancer Prevention meeting in November 2012.

All of the milestones for Task #2 (successful completion of lab work and raw data deposit at centralized location) have been completed.

Task 3. Final Data Analyses, Months 25-36:

1. Clean data, merge all data from different sources by study ID
 - a. The genotyping data were cleaned in Year 3. All other data have been cleaned and merged by study ID.
2. Perform all exploratory analyses to test for adherence to model assumptions
 - a. Preliminary analyses have been performed.
3. Conduct analyses of study data; test study hypotheses
 - a. Statistical analyses have been performed examining associations between 25(OH)D, 1,25(OH)₂D, genetic polymorphisms and prostate cancer aggressiveness.
4. Present preliminary results at scientific meetings

Progress Report Year 3

- a. Two abstracts have been submitted and presented as poster presentations at AACR meetings as listed below and provided in the Appendix.
5. Prepare and submit manuscripts for publication
 - a. One manuscript has been submitted for publication as listed below. Other manuscripts are in preparation.
6. Archive datasets for future analyses
 - a. This activity will be accomplished following completion of primary analyses.
7. Plan future studies
 - a. Planning for future studies has been ongoing and will continue in the final year of the project (and beyond).
8. Drs. Steck and Johnson attend PCRP IMPaCT Annual Meeting or other scientific meeting
 - a. There was no IMPaCT meeting in Year 3. Dr. Steck attended the AACR Science of Cancer Health Disparities meeting in December 2013 and presented a poster of results related to this project (see reference listed below and abstract and results provided in the Appendix).

All of the Milestones for Task #3 (generate final analytic dataset, perform analyses for Specific Aims, present results at scientific meetings, submit manuscripts for publication) have been completed, and data analyses and manuscript development continue. One abstract was presented at the AACR annual meeting in April 2013, and another was presented at the AACR The Science of Cancer Health Disparities meeting in December 2013 (see abstracts and results provided in the Appendix). A manuscript describing the association between 25(OH)D and prostate cancer aggressiveness has been submitted for publication. Other manuscripts are in development.

KEY RESEARCH ACCOMPLISHMENTS, YEAR 3:

- Hired graduate assistant at USC.
- Presented abstract at AACR Science of Cancer Health Disparities 2013 meeting.
- Arranged for shipment of DNA samples to Roswell Park Cancer Institute for genotyping.
- Identified tagSNPs and functional SNPs in genes related to vitamin D metabolism or activity.
- Conducted genotyping (by Roswell Park Cancer Institute).
- Merged and cleaned genotyping data.
- Conducted data analyses of association between gene polymorphisms and prostate cancer aggressiveness.
- Submitted manuscript for publication reporting the association between 25(OH)D and prostate cancer aggressiveness (currently under review at PLoS ONE).

REPORTABLE OUTCOMES:

Presentations (abstracts are attached at the end of this document):

1. Woloszynska-Read, A., Arab, L., Adams, J., Bensen, J., Fontham, E.T.H., Mohler, J.L., Su, L.J., Tabung, F., Zhang, H., Trump, D., Johnson, C., Steck, S.E. Plasma 25-hydroxyvitamin D Levels are Associated with Aggressive Prostate Cancer among African Americans in the North Carolina-Louisiana Prostate Cancer Project (PCaP). In: Proceedings of the 104th Annual Meeting of the American Association for Cancer Research; 2013 Apr 6-10; Washington, DC. Philadelphia (PA): AACR; Abstract #LB-12, 2013. Poster presentation.
2. Steck, S.E., Woloszynska-Read, A., Arab, L., McMahon, D.M., Bensen, J.T., Adams, J.S., Fontham, E.T.H., Mohler, J.L., Su, L.J., Zhang, H., Trump, D., Johnson, C. Ratio of Plasma 1,25(OH)₂D to 25(OH)D is Inversely Associated with Aggressive Prostate Cancer in African Americans in the North Carolina-Louisiana Prostate Cancer Project (PCaP). American Association for Cancer Research The Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved. Atlanta, GA. December 2013. Poster presentation.

Manuscripts in preparation:

1. **Steck, S.E.**, Arab, L., Zhang, H., Bensen, J., Fontham, E.T.H., Johnson, C., Mohler, J.L., Smith, G., Su, L.J., Trump, D., Woloszynska-Read, A. Plasma 25-hydroxyvitamin D, Ancestry and Aggressive Prostate Cancer among African Americans and European Americans in PCaP. Submitted.

CONCLUSION:

During the final no-cost extension year, it is anticipated that data analyses for all specific aims will be completed. Additional manuscripts are being planned. With the large representation of African Americans in this investigation, the proposed research has tremendous potential to provide insights into a chronically underserved population carrying an unequal burden of disease. By examining modifiable biomarkers of risk of aggressive disease and genetic susceptibility by race, this study will impact the identification of subjects at high risk for advanced disease and aid in the design of interventions to target those individuals who will receive the most benefit.

APPENDIX:

Abstract presented at AACR Annual Meeting 2013 (table of results on next page):

Title: Plasma 25-hydroxy vitamin D is associated with aggressive prostate cancer among African Americans in North Carolina-Louisiana Prostate Cancer Project (PCaP).

Authors: Anna Woloszynska-Read, Lenore Arab, Jeannette T. Bensen, John Adams, Elizabeth T.H. Fontham, James L. Mohler, L. Joseph Su, Fred Tabung, Hongmei Zhang, Donald Trump, Candace Johnson, Susan E. Steck.

Background: Experimental and ecological studies support links between vitamin D and prostate cancer prevention and prognosis; however, epidemiologic study results are inconsistent. Given the lower levels of circulating 25hydroxyvitamin D [25(OH)D] and higher prostate cancer aggressiveness, incidence, and mortality among African Americans compared to other racial/ethnic groups, the aim of this investigation was to examine the relationship between plasma 25(OH)D and prostate cancer aggressiveness among African Americans and European Americans.

Methods: Plasma 25(OH)D was measured using LC/MS/MS in 537 African-American and 663 European-American newly-diagnosed prostate cancer patients from the North Carolina-Louisiana Prostate Cancer Project (PCaP). Men were classified as cases (high aggressiveness) if Gleason sum ≥ 8 , or PSA > 20 ng/ml, or Gleason sum ≥ 7 AND clinical stage = T3c-T4c, or Gleason sum=7 with a pattern of (4+3). The comparison group (low aggressiveness) included men with Gleason sum < 7 AND Stage T1-T2 AND PSA < 9 ng/ml. Plasma 25(OH)D was categorized into tertiles based on distributions among low aggressive cases in each race separately. Odds ratios (OR) and 95% confidence intervals (95%CI) were calculated for high aggressive prostate cancer by tertile of plasma 25(OH)D using logistic regression with adjustment for potential confounders.

Results: African Americans had lower mean concentrations of 25(OH)D compared to European Americans (17.7 ± 7.6 and 24.6 ± 9.6 ng/ml, respectively). The highest tertile and middle tertile when compared to the lowest tertile of plasma 25(OH)D were positively associated with highly aggressive prostate cancer among African Americans after adjustment for age, season, education, physical activity, smoking status, and PSA screening history (OR=1.7, 95%CI= 1.0, 2.8 and OR=1.8, 95%CI=1.1, 3.0, respectively). No substantial associations were observed in European American men.

Conclusions: Plasma 25(OH)D was positively associated with prostate cancer aggressiveness among African Americans but not European Americans, such that subjects with highly aggressive prostate cancer had increased odds of having higher plasma 25(OH)D. Blood samples were collected after diagnosis, thus it is possible that effects of treatment or extent of disease or associated processes (e.g. weight loss) on plasma 25(OH)D may explain the findings. Our ongoing studies include analysis of vitamin D binding protein (DBP) in the plasma and genotyping of DBP affinity variants in PCaP subjects. This approach may explain the differences seen in AA and EA men with prostate cancer, as DBP has been implicated in modulating the impact of vitamin D status on prostate cancer.

Table 1. Age- and multivariable-adjusted odds ratios and 95% confidence intervals for high aggressive prostate cancer by tertiles of plasma 25(OH)D3 (final results included in the submitted manuscript which differ slightly from the abstract above due to differences in covariates included in the models).

	25(OH)D3 tertiles, ng/ml	n (high aggressive/ low aggressive)	Age- adjusted odds ratio	Age-adjusted 95% CI	Fully adjusted ^a odds ratio	Fully adjusted ^a 95% CI	Fully adjusted ^a trend test p-value
African Americans	< 13.30	56/102	1.00	referent	1.00	referent	0.27
	13.30 ≤ T2 < 18.90	76/100	1.40	0.89, 2.18	1.80	1.10, 2.96	
	≥ 18.90	81/104	1.36	0.88, 2.11	1.46	0.89, 2.39	
European Americans	< 21.14	67/155	1.00	referent	1.00	referent	0.71
	21.14 ≤ T2 < 26.67	58/150	0.90	0.59, 1.37	0.92	0.59, 1.43	
	≥ 26.67	60/151	0.88	0.58, 1.34	0.92	0.58, 1.44	

^aAdjusted for age, African ancestry, BMI, total energy intake, alcohol intake, physical activity, smoking status, educational status, PSA screening history, study site, NSAIDs use, and season of blood draw

Abstract presented at AACR The Science of Cancer Health Disparities 2013 Meeting (tables of results on next pages):

Title: Ratio of plasma 1,25(OH)₂D to 25(OH)D is inversely associated with aggressive prostate cancer in African Americans in the North Carolina-Louisiana Prostate Cancer Project (PCaP).

Authors: Susan E. Steck, Anna Woloszynska-Read, Lenore Arab, Daria McMahon, Jeannette T. Bensen, John Adams, Elizabeth T.H. Fontham, James L. Mohler, L. Joseph Su, Hongmei Zhang, Donald Trump, Candace Johnson.

Introduction: Epidemiologic studies have reported conflicting results when examining the relationship between circulating vitamin D metabolites and risk of advanced prostate cancer. While 25-hydroxy vitamin D [25(OH)D] is used as a measure of vitamin D status, 1,25-dihydroxy vitamin D [1,25(OH)₂D] is the biologically active form and its concentration is tightly regulated. We previously reported increased odds of aggressive prostate cancer among African Americans in the highest tertile of plasma 25(OH)D compared to the lowest, and have now examined plasma 1,25(OH)₂D and the ratio of 1,25(OH)₂D to 25(OH)D in relation to prostate cancer aggressiveness.

Methods: Plasma 1,25(OH)₂D and 25(OH)D were measured using LC/MS/MS in 435 African-American and 563 European-American men with newly-diagnosed prostate cancer from the North Carolina-Louisiana Prostate Cancer Project (PCaP). Men were classified as highly aggressive cases at time of diagnosis if Gleason sum ≥ 8 , or PSA >20 ng/ml, or Gleason sum ≥ 7 AND clinical stage = T3-T4, or Gleason sum = 7 with a pattern of (4+3). The comparison group (low aggressiveness) included men with Gleason sum <7 AND Stage T1-T2 AND PSA <9 ng/ml. Plasma 1,25(OH)₂D and the ratio of plasma 1,25(OH)₂D to 25(OH)D were categorized into tertiles and quartiles, respectively, based on distributions among low aggressive research subjects in each race separately. Odds ratios (OR) and 95% confidence intervals (95%CI) were calculated for high aggressive prostate cancer by tertiles of 1,25(OH)₂D or quartiles of the 1,25(OH)₂D:25(OH)D ratio using logistic regression with adjustment for potential confounders.

Results: Plasma 1,25(OH)₂D was not associated with odds of aggressive prostate cancer in either African Americans or European Americans in this study (OR=0.83, 95%CI=0.49, 1.41 and OR=0.67, 95%CI=0.40, 1.11, respectively, for highest tertile compared to lowest tertile). However, higher quartiles (as compared to the lowest quartile) of 1,25(OH)₂D:25(OH)D ratio were associated with reduced odds of high aggressive disease among African Americans after adjustment for age, season, education, alcohol intake, smoking status, PSA screening history, physical activity, energy intake, use of non-steroidal anti-inflammatory drugs, study site and body mass index (OR=0.51, 95%CI=0.28, 0.91; OR=0.41, 95%CI=0.22, 0.76, and OR=0.46, 95%CI=0.25, 0.84 for 2nd, 3rd and 4th quartiles, respectively). Inverse associations were also observed for European Americans, but were not statistically significant (OR=0.64, 95%CI=0.35, 1.17 for 4th compared to 1st quartile).

Conclusions: The ratio of plasma 1,25(OH)₂D to 25(OH)D was inversely associated with prostate cancer aggressiveness among African Americans. Blood samples were collected after diagnosis, thus, it is possible that effects of treatment or extent of disease or associated processes (e.g., weight loss) on plasma vitamin D metabolites may have affected their measurement. Future analyses in PCaP will include examining circulating parathyroid hormone, calcium and phosphorus, as well as genotyping of genes encoding enzymes involved in the vitamin D metabolism and activity, which may help to explain these findings.

Tables of results follow:

Table 2. Crude and adjusted odds ratios for aggressive prostate cancer by quartiles of 1,25(OH)₂D:25(OH)D index by race

Quartiles, Vitamin D metabolite index ^a	Case/controls ^b	Crude OR ^c	95%CI ^c	Adjusted OR ^d	95%CI ^d
African-Americans					
1	69/64	1.00	Ref.	1.00	Ref.
2	38/64	0.52	0.31-0.89	0.51	0.28-0.91
3	28/65	0.44	0.25-0.77	0.41	0.22-0.76
4	35/64	0.57	0.33-1.00	0.46	0.25-0.84
European-Americans					
1	41/106	1.00	Ref.	1.00	Ref.
2	38/104	1.00	0.58-1.70	1.09	0.63-1.90
3	33/106	0.88	0.51-1.53	0.92	0.53-1.62
4	25/106	0.66	0.37-1.19	0.64	0.35-1.17

^aQuartiles cutpoints of vitamin D metabolite index:

African-Americans: $Q1 < 0.0013449538$, $0.0013449538 \leq Q2 < 0.0018073957$; $0.0018073957 \leq Q3 < 0.0022770399$; $Q4 \geq 0.0022770399$

European-Americans: $Q1 < 0.0010135403$, $0.0010135403 \leq Q2 < 0.001248328$; $0.001248328 \leq Q3 < 0.0015520382$; $Q4 \geq 0.0015520382$

^bOnly participants with complete observations for all confounders were included.

^cAdjusted for age (categorical)

^dAdjusted for age (categorical), education status, alcohol intake, smoking status, season of the blood draw, PSA screening history, physical activity, energy intake, NSAIDs use, study site and BMI

We have 1,25(OH)₂D data on only 1,000 of the 1,200 men in our ancillary study due to limited plasma availability. Thus, we redid the analyses of 25(OH)D in this subset of 1,000 men to verify that we obtain the same results as with the 1,200 men (Table 3), and we examined the association between 1,25(OH)₂D and aggressiveness and found no significant associations after adjustment for important confounders (Table 4).

Table 3. Plasma 25(OH)D and prostate cancer aggressiveness by race in subset of 1000 men (similar results to those with all 1200 men in ancillary study shown in Table 1)

Race	25(OH)D Tertiles	n (high+intermediate aggressive/low aggressive)	Age-adjusted OR ^a	Adjusted 95% CI ^a	Adjusted OR ^b	Adjusted 95% CI ^b
AAs	tertile1	49/86	1.00	Ref.	1.00	Ref.
	tertile2	52/85	1.15	0.69-1.91	1.59	0.90-2.80
	tertile3	74/89	1.41	0.88-2.27	1.77	1.03-3.06
	Cutpoints: T1<12.93, 12.93 ≤ T2 < 18.32, T3 ≥18.32 ng/ml					
EAs	tertile1	49/139	1.00	Ref.	1.00	Ref.
	tertile2	45/140	0.95	0.59-1.53	1.01	0.61-1.67
	tertile3	45/144	0.85	0.53-1.38	0.90	0.53-1.51
	Cutpoints: T1<20.88, 20.88 ≤ T2 < 26.08, T3 ≥26.08 ng/ml					

^aAdjusted for age (categorical)^bAdjusted for age (categorical), education status, alcohol intake, smoking status, season of the blood draw, PSA screening history, physical activity, energy intake, NSAIDs use, study site and BMI.**Table 4. Plasma 1,25(OH)₂D and prostate cancer aggressiveness by race in subset of 1000 men**

Race	1,25(OH) ₂ D Tertiles	n (high+intermediate aggressive/low aggressive)	Age-adjusted OR ^a (95% CI)	Adjusted 95% CI ^a	Adjusted OR ^b	Adjusted 95% CI ^b
AAs	tertile1	69/85	1.00	Ref.	1.00	Ref.
	tertile2	50/86	0.73	0.45-1.18	0.66	0.39-1.12
	tertile3	56/89	0.88	0.55-1.42	0.83	0.49-1.41
	Cutpoints: T1<23.98, 23.98 ≤ T2 < 31.18, T3 ≥31.18 pg/ml					
EAs	tertile1	61/141	1.00	Ref.	1.00	Ref.
	tertile2	40/140	0.67	0.42-1.08	0.68	0.41-1.11
	tertile3	38/142	0.65	0.40-1.06	0.67	0.40-1.11
	Cutpoints: T1<25.40, 25.40 ≤ T2 < 32.50, T3 ≥32.50 pg/ml					

^aAdjusted for age (categorical)^bAdjusted for age (categorical), education status, alcohol intake, smoking status, season of the blood draw, PSA screening history, physical activity, energy intake, NSAIDs use, study site and BMI.